Remarks

Claims 24-33 and 48-57 are pending. Claims 1-23 and 34-47 are canceled. Applicants reserve the right to pursue the subject matter of all canceled claims in one or more continuation or divisional applications.

Rejections under 35 U.S.C. § 101

Claims 24-33 and 48-57 remain rejected under 35 U.S.C. § 101 because the claimed polypeptide is allegedly not supported by a specific, substantial and credible or well established utility. More specifically, in comparison to *In re* Brana, the Examiner alleges that, "[n]o *in vitro* tests for any specific activity are set forth in the [present] specification for the claimed polypeptides," and, "[t]he instant specification discloses no similar polypeptides having any well established utilities." *See* present Office Action, mailed February 9, 2005, page 2, 8th paragraph.

Considering the second point first, Applicants submit that with respect to at least one well-established utility, the only relevant "similar polypeptides" necessary are examples of those useful as tissue-specific markers for the diagnosis, detection, prevention and/or treatment of particular types of cancer. Indeed, cancer markers such as these were well-known and used in the art as of the earliest effective priority date in the present application. For example, Yoshida, *et al.* and Lyubsky, *et al.*, (Exhibits A and B) describe the characterization of molecular markers for the diagnosis of hepatocellular carcinoma and pancreatic cancer; moreover, Rajkumar, *et al.*, and Maeda, *et al.* (Exhibits C and D) describe the characterization of molecular markers for distinguishing hepatocellular carcinoma from metastatic liver cancer. Thus, even though Applicants' invention may not yet be ready for use in the clinic, it meets the 35 U.S.C. § 101 utility standard.

With regard to the first point, Applicants respectfully disagree. However, Applicants are uncertain as to exactly which part of 35 U.S.C. §101 is allegedly deficient in the asserted utility, *i.e.*, is Applicants' utility allegedly not specific, not substantial, or not credible? Applicants respectfully submit that the Examiner appears to return to this issue in a more direct manner on page 3, first paragraph of the current Office Action which states, "...[n]o biological activity of the polypeptide itself is disclosed in the specification. Therefore, there can be no correlation to a disease or condition." With this statement the Examiner appears to be questioning the specificity of Applicants' asserted

utility. Applicants respectfully disagree and traverse.

As a preliminary matter, Applicants point out that according to section 2107.01 of the M.P.E.P., where Applicants disclose a biological activity, and reasonably correlate that activity to a disease or condition, Applicants have sufficiently identified a specific utility for this invention. (*See* M.P.E.P. 8th edition, revision 2, at 2100-32, paraphrased, emphasis added). Stated in other words, so long as the correlation between the biological activity and the asserted use in a particular disease or condition is sufficient to convince one of skill in the art, then the specificity requirement of 35 U.S.C. § 101 is satisfied.

The present specification discloses a specific biological activity for HFVAB79: "[t]his gene is expressed primarily in the liver, and to a lesser extent, in testis," a statement which is supported by Table 2, page 291, row 8 which lists the tissue/cell libraries in which HFVAB69 was detected, HO151 = early stage human liver, H0574 = hepatocellular tumor, re-excision, and H0038 = early stage testis libraries. In light of this disclosure, Applicants respectfully submit that one of ordinary skill in the art would conclude that a reasonable correlation exists between the tissue/cells in which HFVAB79 expression was detected, and Applicants asserted utility, as stated below (emphasis added):

> The tissue distribution in liver tissue indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention and/or treatment of liver disorders, particularly those affecting the immune and hematopoietic systems, including hepatomas. Representative uses are described in the "Hyperproliferative Disorders," "Infectious Disease," and "Binding Activity" sections below, in Example 11, and 27, and elsewhere herein. Briefly, polynucleotides and/or polypeptides corresponding to this gene can be used for the detection, treatment, and/or prevention of hepatoblastoma, jaundice, hepatitis, or liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells. *See* specification page 29, paragraph 78, first 3 sentences.

Therefore, Applicants respectfully submit that the asserted utility is specific.

The Examiner has also questioned the credibility of Applicants asserted utilities, alleging that, "...the length and diversity of potential activities, and utilities enumerated in the specification leaves it to one of skill in the art to determine which is credible...such determinations would require further inventive research beyond the disclosures of the specification." *See* present Office Action, paragraph bridging pages 2-3. Applicants

respectfully disagree.

As a preliminary matter, Applicants point out that the M.P.E.P. instructs that "[c]redibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record" and that "[a]n applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement." (See, M.P.E.P. § 2107 at II.B.(1)(ii)).

As discussed in Applicants' response of September 28, 2004, the utilities asserted for HFVAB79 are based upon the specific properties of the claimed polypeptide, *e.g.*, expressed primarily in the liver and also expressed in hepatocellular tumor, re-excision, and the asserted utilities are interrelated, *e.g.*, related to liver physiology and pathology. Moreover, the post filing date publications of Smith, *et al.* (Exhibit E), and Raoult, *et al.* (Exhibit F), corroborate Applicants' asserted utility, *i.e.,* that expression of HFVAB79 can be used, for example, to diagnose hepatocellular carcinoma.

The Examiner also alleges that the post filing date art submitted with Applicants' previous response goes "...beyond the experiments proposed in the specification, and the art fails to shed light on any utility known at the priority date accorded the claims." *See* present Office Action, page 3, 2nd paragraph. Applicants respectfully disagree. The present specification teaches that "[p]olynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hepatic, reproductive, or endocrine disorders, particularly hepatoma or male infertility." *See* page 29, paragraph 77 (emphasis added). The post filing date art of Smith, *et al.* (*See* Exhibit E, page 863, left column, lines 9-13) and Raoult, *et al.* (*See* Exhibit F, page 11501, left column, last two full sentences and Figure 7), corroborate this assertion.

While the Examiner alleges the publications of Smith, *et al.*, and Raoult, *et al.*, "go beyond the experiments proposed" in Applicants' specification, Applicants respectfully submit that one of ordinary skill in the art would agree that Applicants' observation that HFVAB79 is expressed primarily in the liver is supported by the post filing date art (*See* Smith, *et al.*, page 862, Fig. 3 and page 863, left column, lines 9-13; Raoult, *et al.*, page 11500, Fig. 5). Furthermore, Applicants' observation that HFVAB79 is also expressed in hepatocellular carcinoma, re-excision, supports Applicants' asserted

utility. *At the very least*, one of ordinary skill in the art would recognize that given a liver-localized cancerous growth, Applicants invention provides a potential molecular marker[1] for helping to distinguish whether the liver-localized cancerous growth is a hepatocellular carcinoma (also known as a primary cancer) or a cancer that has metastasized to the liver from elsewhere in the body. Molecular markers that can distinguish hepatocellular carcinoma from metastatic liver cancer are of particular importance due to the fact that "[t]he liver and lungs share the dubious distinction of being the visceral organs most often involved in the metastatic spread of cancers. Indeed, *the most common hepatic neoplasms are metastatic carcinomas* with colon, lung, and breast heading the list as sites of the primary tumor." (*See* Exhibit G, Kumar et. al., Basic Pathology, 6th edition, page 547, right column, emphasis in the original). Since each type of liver cancer is treated differently, *i.e.*, local treatment, such as excision, for hepatocellular carcinoma versus systemic treatment, such as chemotherapy, for metastatic liver cancer, the ability to distinguish hepatocellular carcinoma from metastatic liver cancer is important. Indeed, the identification of molecular markers that can be used to make this determination was a well known challenge as of Applicants' earliest effective priority date, as illustrated by the publications of Rajkumar, *et al.*, and Maeda, *et al.* (*See* Exhibits C and D, page 533, left column, first paragraph, and page 901, right column, first paragraph, respectively). Moreover, molecular markers for hepatocellular carcinoma continue to be refined, as shown, for example, by the recent publication of Saad, *et al.* (*See* Exhibit H, page 1, abstract and right column, first paragraph).

Thus, Applicants respectfully submit that the use of HFVAB79 polypeptide to generate or select antibodies that can be used to detect or diagnose hepatocellular carcinoma, for example to distinguish hepatocellular carcinoma from metastatic liver cancer, is a specific, substantial and credible utility which is supported by Applicants' specification, for example, the paragraph bridging pages 29-30.

With regard to the remainder of the Examiner's 35 U.S.C. § 101 rejection, from page 3, 3rd paragraph to page 6, 1st paragraph, Applicants note that this is substantially identical to the rejection given in the previous Office Action dated June 29, 2004 (*See*

[1] As described on specification page 289, paragraph 740, "Table 2 summarizes the expression profile of polynucleotides...Expression of these polynucleotides [HFVAB79] was not observed in the other tissues and/or cell libraries tested. One of skill in the art could routinely use this information to identify tissues which show a predominant expression pattern of the corresponding polynucleotide of the invention [HFVAB79]..."

page 3, second paragraph to page 6, second paragraph). As Applicants answered each aspect of the 35 U.S.C. § 101 rejection put forth in the Office Action of June 29, 2004 in the response submitted September 28, 2004, Applicants respectfully request that the Examiner reconsider the response submitted September 28, 2004.

In light of the reasoning given above, Applicants respectfully request that the rejection under 35 U.S.C. § 101 be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 24-33 and 48-57 have been rejected under 35 U.S.C. § 112, first paragraph because the claimed invention is allegedly "...not...supported by a specific, substantial, and credible utility...or a well-established utility...one skilled in the art clearly would not know how to use the claimed invention." *See* present Office Action page 6, second paragraph.

Applicants respectfully disagree and traverse. The Examiner "should not impose a 35 U.S.C. § 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. §101 rejection is proper." M.P.E.P. § 2107 (IV) at 2100-36. As explained above, claims 24-33 and 48-57 comply with the utility requirement of 35 U.S.C. § 101. Accordingly, Applicants respectfully request that rejection of claims 24-33 and 48-57 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Conclusion

Applicants respectfully request that the above-made remarks be entered and made of record in the file history of the instant application. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicants would expedite the examination of this application. In view of the explanations provided herein, Applicants respectfully request an interview with the Examiner to more full clarify any outstanding issue prior to issuance of any subsequent final Office Action.

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 that is not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Dated: April 5, 2005

Respectfully submitted,

By _____

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